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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,984	07/01/2002	Thomas Frank Bumol	X-13199	3218

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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,984	BUMOL ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,10 and 13-18* is/are pending in the application.

4a) Of the above claim(s) *4-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants' Amendment, filed 6 December 2005, is acknowledged. Claims 1-3, 9, and 11-12 were cancelled. Claims 4-8, 10, and 13-18 are pending. Claims 4-7 are withdrawn, as drawn to a non-elected invention. Claims 8, 10, and 13-18 are under examination.

Response to Arguments

Claim Rejections/Objections Withdrawn

2. The rejection of claims 1-3, 9 and 11 under 35 USC 112, first paragraph is moot in view of Applicants' cancellation of claims 1-3,9, and 11. Applicants' arguments, see Remarks, filed 6 December 2005, with respect to claims 1-3, 9, and 11 under 35 USC 112, first paragraph, scope of enablement, have been considered but are moot in view of the Applicants' cancellation of claims 1-3, 9, and 11.

3. The rejection of claims 1-3 and 12 under 35 USC 102(e), is moot view of the Applicants' cancellation of claims 1-3 and 12. Applicants' arguments, see Remarks, filed 6 December 2005, with respect to claims 1-3 and 12 under 35 USC 102(e), have been considered but are moot in view of the Applicants' cancellation of claims 1-3 and 12.

Applicant's arguments with regard to claims 8, 10, and 13-18 are moot, as these claims were not been rejected under 35 USC 102 in the prior Office Action.

It is noted that the Office Action of 18 January 2005 cites the statutory authority for 102(e), but mistakenly recites "102(b)" in the preamble of the rejection. For clarification of the record, the Ashkenazi *et al.*, reference is 102(e) art, not 102(b).

Claim Rejections/Objections Maintained

4. It is noted that no correction has been made to the specification regarding the objections made related to the use of Trademarks in the specification.

New Grounds of Rejection, Necessitated by Amendment

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The rejection of claim 8 under 35 USC 103(a), as unpatentable over Ashkenazi *et al.*, in view of Hagimoto *et al.*, and the rejection of claim 10 under 35 USC 103(a), as unpatentable over Ashkenazi *et al.*, in view of Yamamoto *et al.*, are withdrawn in light of the new grounds of rejection which follow. Claims 9 and 11 have been cancelled. Applicants' arguments have been fully considered but are moot in view of the new grounds of rejection which follow.

7. Claims 8, 13, 14, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Askenazi (US Patent Publication 2002/0065210, priority to 18 September 1997), in view of Hagimoto *et al.*, Am J Respir Cell Mol Biol. 1997 17(3)272-278), and Deen *et al.*, US Patent 6,313,269 (6 November 2001, priority to 14 March 1999).

Claim 8 is drawn to a method for treating pulmonary fibrosis in a patient comprising parental administration of FLINT at a dose of 1μg/kg/day to 10mg/kg/day. Claim 13 is drawn to a method as in claim 8, wherein the dose is 2 mg/kg/day to 4mg/kg/day. Claim 14 is drawn to a method as in claim 13, wherein said dose is 2.5 mg/kg/day. Claim 17 is drawn to a method for treating pulmonary fibrosis in a patient comprising continuous infusion of FLINT at a dose of 0.1 μg/kg/hour to about 50μg/kg/hour.

Ashkenazi *et al.*, teach a molecule designated DcR3 (also known as TR6, and decoy receptor 3 for FAS ligand, which has 100% sequence identity to the claimed "FLINT" polypeptides) that inhibits binding between FASL and FAS (p. 5, paragraph 0064). Ashkenazi *et al.*, do not teach use of DcR3 in pulmonary fibrosis or dosage ranges for administration of DcR3.

Hagimoto *et al.*, teach increased levels of apoptosis and increased mRNA levels of FASL/FAS mediate pulmonary fibrosis (pp. 98-99, Figures 3-4). Hagimoto *et al.*, also teach corticosteroid inhibition of FAS/FASL mRNA in pulmonary fibrosis (p. 100, column 1, last paragraph). Hagimoto *et al.*, do not teach dosage ranges for administration of DcR3.

Deen *et al.*, teach soluble TR6 polypeptides (also known as DcR3, and decoy receptor for FAS ligand, (see i.e. attached synonymns for TNFRSF68 from Information Hyperlinked Over Proteins – IHOP) in dose ranges of 0.1-100 μg/kg (column 29, lines 38-39), intravenous administration (IV) at 1mg/kg and subcutaneous administration at 3mg/kg (column 31, lines 20-25), with a lower limit of dose concentration at 1.0 ng/ml in the pharmacokinetics studies. Deen *et al.*, do not teach pulmonary fibrosis.

Animal models of pulmonary fibrosis were well known in the art at the time the application was filed. It was also well known in the art at the time the application was filed, that apoptosis through the FAS/FASL signaling pathway was critical to disease progression. Hagimoto *et al.*, demonstrated this

connection in an animal model of pulmonary fibrosis by using corticosteroids to downregulate FAS/FASL mRNA, resulting in the apoptosis of infiltrating T-cells (p. 100, column 1, last paragraph to column 2, first paragraph). Hagimoto *et al.*, specifically demonstrate that continuous epithelial apoptosis caused by persistent FASL mRNA expression and upregulation of FAS mRNA may result in excessive cell death of epithelial cells, which overwhelms the clearing necessary to maintain homeostasis (p. 101, first column, second paragraph). Moreover, Hagimoto *et al.*, explain that the FAS/FASL system and apoptosis plays an important role in recovering from an acute lung injury and that it also participates in damaging tissue by causing excessive apoptosis through its continuous and extensive expression (p. 101, first column, second paragraph). Thus, one of ordinary skill in the art would be motivated to combine the teachings of Askenazi *et al.*, using the DcR3/FASL decoy receptor with the teachings of Hagimoto *et al.*, who show that substances that disrupt and decrease the FAS/FASL system decrease the cell death associated with apoptosis in pulmonary fibrosis. The skilled artisan would have reasonably expected success because Hagimoto *et al.*, has been successful in using corticosteroids in an animal model of pulmonary fibrosis and Askenazi *et al.*, demonstrated the inhibition of FASL signaling using DcR3. The intended use of the claimed molecules does not change the patentability of the molecules. Additionally, one of ordinary skill in the art would be motivated to use the dosages of Deen *et al.*, because Deen *et al.*, had already demonstrated the pharmacokinetics of a TR6-Ig fusion protein and found dose ranges at which maximal plasma concentrations were observed after dosing. The skilled artisan would have reasonably expected success with dosages of TR6/DcR3/FLINT at the dosage levels cited by Deen *et al.*, because Deen *et al.*, were successful and showed that the Tr6-Fc protein was well absorbed and tolerated at those levels and that the kinetics of the polypeptide were acceptable for *in vivo* use.

8. Claims 10, 15, 16, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Askenazi (US Patent Publication 2002/0065210, priority to 18 September 1997) in view of Yamamoto *et al.*, (Chest 1997 112(2):505-510), Hebestrein *et al.*, (Eur J Immunol 1996 26:8:1775-1780), and Deen *et al.*, US Patent 6,313,269 (6 November 2001, priority to 14 March 1999).

Claim 10 is drawn to a method for treating COPD in a patient comprising parental administration of FLINT at a dose of 1μg/kg/day to 10mg/kg/day. Claim 15 is drawn to a method as in claim 10, wherein the dose is 2 mg/kg/day to 4 mg/kg/day. Claim 16 is drawn to a method as in claim 15, wherein said dose is 2.5 mg/kg/day. Claim 18 is drawn to a method for treating pulmonary fibrosis in a patient comprising continuous infusion of FLINT at a dose of 0.1 μg/kg/hour to about 50μg/kg/hour.

Ashkenazi *et al.*, teach a molecule designated DcR3 (also known as TR6, and decoy receptor 3 for FAS ligand, which has 100% sequence identity to the claimed "FLINT" polypeptides) that inhibits binding between FASL and FAS (p. 5, paragraph 0064). Ashkenazi *et al.*, do not teach use of DcR3 in pulmonary fibrosis or dosage ranges for administration of DcR3.

Yamamoto *et al.*, teach elevated markers of eosinophils (i.e. increased eosinophils) accompany COPD (p. 508, figure 3). Yamamoto et al., do not teach DcR3/TR6.

Hebestreit *et al.*, teach that eosinophils express FAS receptor and can mediated increased apoptotic cell death (p. 1777-1778; Figures 2-3). Hebestreit *et al.* do not teach COPD.

Deen *et al.*, teach soluble TR6 polypeptides (also known as DcR3, and decoy receptor for FAS ligand; see *i.e.* attached synonyms for TNFRSF68 from Information Hyperlinked Over Proteins – IHOP) in dose ranges of 0.1-100 μg/kg (column 29, lines 38-39), intravenous administration (IV) at 1mg/kg and subcutaneous administration at 3mg/kg (column 31, lines 20-25), with a lower limit of dose concentration at 1.0 ng/ml in the pharmacokinetics studies. Deen *et al.*, do not teach COPD.

It was well known in the art at the time the application was filed, that apoptosis occurred through the FAS/FASL signaling pathway was critical to disease progression. One of ordinary skill in the art would be motivated to combine the teachings of Askenazi *et al.*, using the DcR3/FASL decoy receptor/FLINT polypeptide with the teachings of Yamamoto *et al.*, and Hebestreit et al., who show that the FAS receptor mediates increased apoptotic cell death in individuals with COPD. Additionally, one of ordinary skill in the art would be motivated to use the dosages of Deen *et al.*, because Deen *et al.*, had already demonstrated the pharmacokinetics of a TR6-Ig fusion protein and found dose ranges at which maximal plasma concentrations were observed after dosing. The skilled artisan would have reasonably expected success with dosages of TR6/DcR3/FLINT at the dosage levels cited by Deen *et al.*, because Deen *et al.*, were successful and showed that the Tr6-Fc protein was well absorbed and tolerated at those levels and that the kinetics of the polypeptide were acceptable for *in vivo* use. Thus, the rejection of claims 8, 13, 14, and 17 is maintained for the reasons of record in the Office Action of 15 January 2005 and for the reasons stated herein.

The skilled artisan would have reasonably expected success because Askenazi *et al.*, demonstrated the inhibition of FASL signaling using DcR3 (FLINT) and Yamamoto *et al.*, and Hebestreit et al., demonstrated that FASL signaling is directly involved in COPD. The intended use of the claimed molecules does not change the patentability of the molecules. Additionally, Deen *et al.*, had already demonstrated the pharmacokinetics of a TR6-Ig fusion protein and found dose ranges at which maximal plasma concentrations were observed after dosing. The skilled artisan would have reasonably expected

success with dosages of TR6/DcR3/FLINT at the dosage levels cited by Deen *et al.*, because Deen *et al.*, were successful and showed that the Tr6-Fc protein was well absorbed and tolerated at those levels and that the kinetics of the polypeptide were acceptable for *in vivo* use.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claims 13-16, the phrase "as in" renders the claims indefinite because it is unclear whether the limitation) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Claims 13-16 recite "a method as in claim 8/13/10/15..." [Emphasis added]. The phrase "as in" is read to be a simile and liken the method of claims 13-16 to claims 8, 10, 13, and 15, but the phrase does not limit the method of claims 13-16 to the afore referenced claims. Thus, the method of claims 13-16 could encompass something outside of the referenced claim.

11. Claims 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "to about" is not limiting.

Conclusion

Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CMW

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